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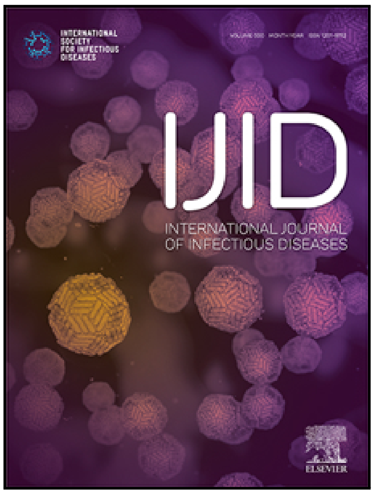

BACTERAEMIC PNEUMOCOCCAL PNEUMONIA AND SARS-CoV-2 PNEUMONIA: DIFFERENCES AND SIMILARITIES

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HIGHLIGHTS:

- In-hospital course and 30-day survival between SARS-CoV-2 and B-PCAP were compared.
- B-PCAP was associated with higher severity on admission and ICU rate.
- SARS-CoV-2 pneumonia related mortality was higher and occurred later.
- Pneumonia severity scales underestimate risk of death in SARS-CoV-2 pneumonia.

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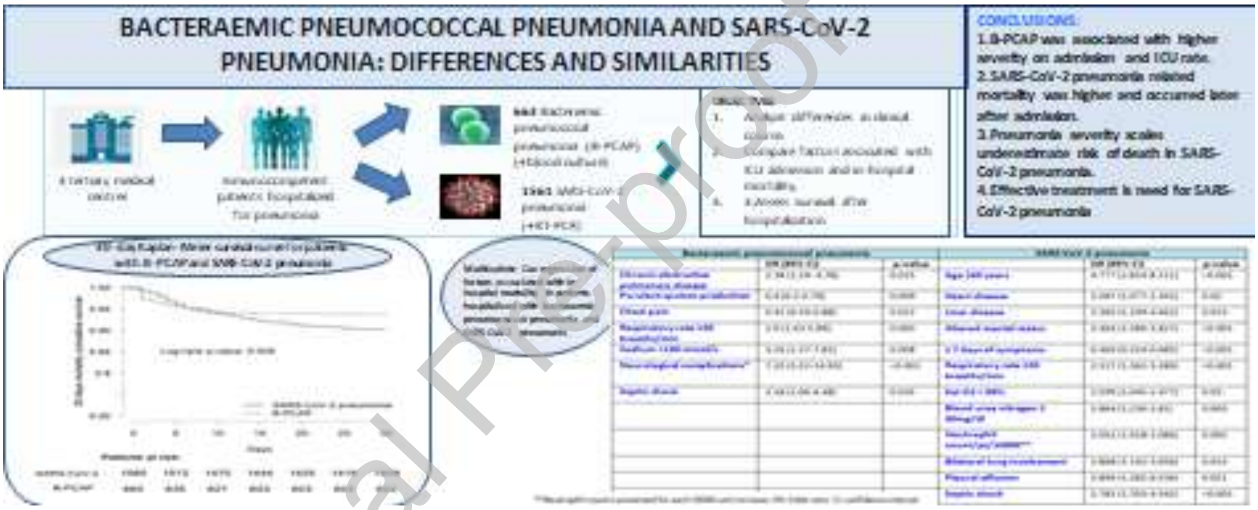
Graphical abstract



Abstract:

Objective: Analyse differences in clinical presentation and outcome between bacteraemic pneumococcal community-acquired pneumonia (B-PCAP), and SARS-CoV-2 pneumonia.

Methods: Observational multicenter study conducted on patients hospitalized for B-PCAP between 2000-2020 and SARS-CoV-2 pneumonia during 2020. We compared 30-day survival, predictors of mortality and intensive care unit (ICU) admission.

Results: We included 663 B-PCAP and 1561 SARS-CoV-2 pneumonia. B-PCAP patients had higher severity, ICU admission and more complications. SARS-CoV-2 pneumonia patients had higher in-hospital mortality (10.8%vs6.8%, p 0.004). Among ICU patients, need for invasive mechanical ventilation (69.7%vs36.2%, p<0.001) and mortality were higher in SARS-CoV-2 pneumonia. In B-PCAP, our predictive model related mortality to systemic complications (hyponatremia, septic shock, neurological complications), lower respiratory reserve or tachypnoea; whereas chest pain and purulent sputum were protective. In SARS-CoV-2, mortality was related to previous liver and cardiac disease, advanced age, altered mental status, tachypnoea, hypoxemia, bilateral involvement, pleural effusion, septic shock, neutrophilia, and high blood urea nitrogen; in contrast, ≥7 days of symptoms was a protective factor. In-hospital mortality occurred earlier in B-PCAP.

Conclusions: Although B-PCAP was associated with higher severity and ICU rate, SARS-CoV-2 pneumonia-related mortality was higher and occurred later. New prognostic scales and more effective treatments are needed for SARS-CoV-2 pneumonia.

Keywords: community acquired pneumonia, bacteraemic pneumococcal pneumonia, SARS-CoV-2, process of care, mortality, survival.

Abbreviation list:

AEMPS:Spanish Agency for Medicines and Health Products

B-PCAP:bacteraemic pneumococcal community-acquired pneumonia

CAP: community-acquired pneumonia

CI: confidence interval

COPD: Chronic obstructive pulmonary disease

CURB-65: Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥65 years

COVID-19: coronavirus disease 2019

CRP: C-reactive protein

ICU: intensive care unit

IMV: invasive mechanical ventilation

OR: Odds Ratio

PSI: Pneumonia Severity Index

RT-PCR: reverse transcription-polymerase chain reaction

SEPAR: Spanish Society of Pulmonology and Thoracic Surgery

Background

Streptococcus pneumoniae remains the most common cause of community-acquired pneumonia (CAP) (Johansson el al., 2010; Van der Pol and Opal, 2009). Among pneumonia pathogens, it is the leading cause of hospitalization and death in adults (Roson et al., 2001; Shariatzadeh et al., 2005).Around 15-25% of cases of pneumococcal pneumonia are bacteraemic (Said et al., 2013) and this form of the disease, bacteraemic pneumococcal pneumonia (B-PCAP), has traditionally been considered an invasive form of infection related to higher inflammatory status, worse in-hospital course and shorter long-term survival (Capelastegui et al., 2014; Ishiguro et al., 2016; Ruiz et al., 2019).

At the end of 2019, novel coronavirus, designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused an international outbreak which started in China and rapidly grew into a global pandemic (Dhama et al., 2020; Zhou et al., 2020). It causes a serious respiratory illness called coronavirus disease 2019 (COVID-19), and has become a public health emergency which has caused over 243 million confirmed cases and more than 4.9 million deaths.

Over the last months, numerous publications have sought to describe the stages of the COVID-19 illness; the clinical course; process of care; and predictive factors for poor outcome in SARS-CoV-2 pneumonia. Nonetheless, few studies have compared clinical features of SARS-CoV-2 and other types of pneumonia (Shi et al., 2021; Tian et al., 2020; Zhao et al., 2020; Zhou et al., 2020).

The aim of our study was to analyse the differences and similarities in clinical presentation, host inflammatory response and outcome between what has previously been the most common and invasive pneumonia (B-PCAP),and the pneumonia caused by the current pandemic virus which is threatening global public health (SARS-CoV-2 pneumonia). We have compared factors associated with intensive care unit (ICU) admission and in-hospital mortality and assessed survival after hospitalization in both types of pneumonia.

Methods

Study design and population

This is an observational multicenter study based on the analysis of a prospective registry of consecutive immunocompetent adults (aged 18 years or more) hospitalized for bacteraemic pneumococcal pneumonia between January 2000 and May 2020 and consecutive immunocompetent patients admitted for SARS-CoV-2 pneumonia between March and December 2020 (1^{st} and 2^{nd} COVID-19 waves) to one of three tertiary medical centres (Cruces University Hospital, La Fe Hospital and Galdakao-Usansolo Hospital) in Spain. This study was approved by the corresponding ethics committee (code PI2020083) and conducted in accordance with the principles of the Declaration of Helsinkion research in humans.

The bacteriological diagnosis of B-PCAP was based on blood culture positive for *S. pneumoniae* taken within 24 h after presentation at hospital. Cases of SARS-CoV-2 pneumonia were confirmed by positive reverse transcription-polymerase chain reaction (RT-PCR) assay for the virus in nasopharyngeal swabs. Patients were excluded if they were known to be positive for human immunodeficiency virus or chronically immunosuppressed or had been hospitalized for the previous 14 days before the diagnosis of pneumonia.

Study variables

We recorded patients' clinical and demographic characteristics, as well as physical examination, laboratory and radiological findings on admission. To assess the severity of pneumonia, we used the Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥65 years (CURB-65) (Lim et al., 2003) and Pneumonia Severity Index (PSI) (Fine et al., 1999) scores. Measures of in-hospital clinical course and outcome included: 1) development of in-hospital complications; 2) admission to the intensive care unit (ICU); 3) use of invasive mechanical ventilation (IMV); 4) septic shock; 5) in-hospital mortality; and 6) length of hospital stay. Treatment of patients with COVID-19was based on the recommendations issued by the Spanish Ministry of Health and the Spanish Agency for Medicines and Health Products (AEMPS) at the time of diagnosis (http://www.aeemt.com/web/wpcontent/uploads/2020/03/4_6026300193912129107.pdf, accessed April 2020; https://www.aemps.gob.es/laAEMPS/docs/medicamentos-disponibles-SARS-CoV-2-19-3-2020.pdf, accessed may 2020; https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%e2%80%9119/tratamientos-disponibles-para-el-manejo-de-la-infeccion-respiratoria-por-sars-cov-2/?lang=en, accessed September 2021; https://www.covid19treatmentguidelines.nih.gov/, accessed September 2020). B-PCAP patients were treated following the guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) (Menendez et al., 2010). In-hospital care and medical care following discharge were determined by patients' healthcare providers.

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrate on chest X-ray together with acute signs and symptoms suggestive of lower respiratory tract infection. The disease was classified as B-PCAP when blood culture was positive for *S. pneumoniae* and SARS-CoV-2 pneumonia when RT-PCR was positive for the SARS-CoV-2 in nasopharyngeal swabs.

Patients were considered active smokers if they smoked at least 10 cigarettes per day and heavy alcohol users if they reported a daily alcohol intake of at least 80 g for men or 60 g for women during the previous year (Grau et al., 2014). Septic shock was defined as a systolic blood pressure < 90 mmHg and the need for vasopressors for 4 hours or more after fluid replacement therapy on admission (Levy et al., 2003).

Statistical analysis

Bivariate tables were constructed for patients with B-PCAP and SARS-CoV-2 pneumonia. Categorical variables were expressed as frequencies and percentages, and continuous variables as means (standard deviations) or medians (interquartile ranges) depending on whether data were normally distributed. For continuous variables, comparisons were performed with Student's t-test if the data followed a normal distribution, and otherwise with a Mann-Whitney U test. Chi-square or Fisher's exact tests were performed for comparing qualitative variables.

Logistic regression models were performed to assess which variables were associated with ICU admission and use of IMV. Cox regression models were built to analyse in-hospital mortality. All variables with a p-value lower than 0.100 in the bivariate analysis were included in logistic regression models. In the multivariate logistic regression model, we eliminated the variables with the highest p-values one-by-one until all the variables entered were significant at p-value <0.05. The results have been expressed as odd ratios (ORs) with corresponding 95% confidence intervals (CI). In the case of COVID-19 patients, multiple imputations were used to impute any missing respiratory rate values.

Patient 30-day survival was analysed using the Kaplan-Meier method. The log-rank test was used to compare survival between groups.

All analyzes were performed with the statistical software R (version 4.0.1).

Results

We enrolled 663 patients hospitalized for B-PCAP and 1561 hospitalized for SARS-CoV-2 pneumonia. Table 1 summarizes the patient baseline characteristics and in-hospital course overall and stratified by pneumonia aetiology. Patients with B-PCAP were older and more likely to have comorbidities. Focusing on clinical presentation, they were more likely to have greater severity of illness, but the median duration of symptoms was shorter (3 vs 7 days, p<0.001). In addition, patients with B-PCAP had worse laboratory findings including higher C-reactive protein (CRP) levels and lower lymphocyte count (median 710 vs 990, p<0.001), but were less likely to have bilateral lung involvement on chest X-ray (16.9% vs 71.8%, p<0.001). Further, the patients with B-PCAP were more frequently classified in the higher risk classes according to CURB-65 (2 to 5) and PSI (4 and 5) scores (p< 0.001). Patients with B-PCAP were more frequently admitted to the ICU (27.9% vs 12.9%, p<0.001); in contrast, the IMV rate was similar in the two groups (10.1% vs 9.1%, p=0.505). A greater percentage of B-PCAP patients had complications during hospitalization; in contrast, SARS-CoV-2 pneumonia patients had higher in-hospital mortality rate (10.8% vs 6.8%, p=0.004 and longer in-hospital stay.

Table 2 shows differences between patients admitted to the ICU with B-PCAP (n=185) vs SARS-CoV-2 pneumonia (n=201). The clinical presentation showed greater severity in patients with B-PCAP pneumonia and they also had higher risk class according to PSI and CURB-65 scores. In contrast, patients with SARS-CoV-2 pneumonia were more likely to have bilateral lung involvement (83.6% vs 34.6%, p<0.001) and receive IMV (69.7% vs 36.2%, p<0.001). Thromboembolic complications, unlike all other complications, were more usual in patients with SARS-CoV-2 pneumonia (12.9% vs

2.2%). SARS-CoV-2 pneumonia patients admitted to the ICU, like the overall sample of patients with this type of pneumonia, had higher in-hospital mortality (23.9% vs 13%, $p=0.009$) and longer in-hospital stay.

The results of multivariate Cox regression of factors potentially associated with in-hospital mortality are listed in Table 3. In a multivariate Cox regression model, the following were independent factors associated with in-hospital mortality in B-PCAP: chronic obstructive pulmonary disease (COPD) (OR: 2.38; 95% CI: 1.19-4.78; $p=0.015$); respiratory rate ≥30 breaths/min (OR: 2.9; 95% CI: 1.43-5.89; $p=0.003$); sodium <130 mmol/L (OR: 3.26; 95% CI: 1.37-7.81; $p=0.008$); neurological complications (OR: 7.25; 95% CI: 3.52-14.93; $p<0.001$) and septic shock (OR: 2.18; 95% CI: 1.06-4.48; $p=0.035$). Purulent sputum production (OR: 0.4; 95% CI 0.2-0.79; $p=0.009$) and chest pain (OR: 0.41; 95% CI: 0.19-0.88; $p=0.022$) were protective factors. In SARS-CoV-2 pneumonia, predictors of in-hospital mortality were age ≥ 65 years (OR: 4.777 ; 95% CI: 2.814-8.111; $p<0.001$), heart disease (OR: 1.587; 95% CI: 1.007-2.341; $p=0.02$),liver disease (OR: 2.365; 95% CI:1.199-4.662); altered mental status (OR: 2.464 ; 95% CI: 1.586-3.827; $p<0.001$), respiratory rate ≥30 breaths/min (OR: 2.117; 95% CI: 1.362-3.289; $p<0.001$); hypoxemia (OR: 1.599 ; 95% CI: 1.045-2.447; $p=0.03$), blood urea nitrogen (BUN) ≥30mg/dL (OR: 1.864 ; 95% CI: 1.236-2.81; $p=0.003$), neutrophilia (each 10000 unit increase in neutrophil count/µL) (OR: 1.052; 95% CI: 1.018-1.086; $p=0.002$), bilateral lung involvement (OR: 1.868; 95% CI: 1.142-3.056; $p=0.013$), pleural effusion (OR: 2.894; 95% CI: 1.282-6.536; $p=0.011$) and septic shock (OR: 2.781; 95% CI: 1.703-4.542; $p<0.001$). 7 or more days of symptoms on admission was protective factor for mortality (OR: 0.464; 95% CI: 0.314-0.685; $p<0.001$). The results of multivariate logistic regression of factors associated with ICU admission and IMV in patients hospitalized with B-PCAP or SARS-CoV-2 pneumonia are reported respectively in Table 4 and Supplementary Table 1.

Figure 1 compares the 30-day Kaplan-Meier survival curves for patients with B-PCAP and SARS-CoV-2 pneumonia. The 30-day survival rate is significantly lower in patients with SARS-CoV-2 pneumonia (90.2% vs 93.8%, long rank p<=0.009).

Discussion

This study provides a comprehensive evaluation of host-related factors, process of care and outcome in a consecutive series of patients diagnosed with B-PCAP and SARS-CoV-2 pneumonia. Our main findings were: 1) Patients with SARS-CoV-2 pneumonia had higher in-hospital mortality despite those with B-PCAP having more comorbidities, a more severe clinical presentation and laboratory findings, and higher ICU admission rates and in-hospital complications. 2) Compared with B-PCAP, patients hospitalized with SARS-CoV-2 pneumonia requiring ICU admission were more likely to receive IMV and had poorer outcomes with a higher mortality rate. 3) Factors and clinical scales (PSI and CURB-65) classically associated with severity and mortality on admission in patients with bacterial community-acquired pneumonia demonstrated lack of predictive value in patients with SARS-CoV-2 pneumonia. 4) B-PCAP was characterized by early in-hospital mortality; in contrast, in SARS-CoV-2 pneumonia, in-hospital mortality occurred later.

Our sample is particularly interesting for several reasons: 1) The types of pneumonia that are compared: the pneumonia that has previously been the most common, invasive and virulent pneumonia which is able to produce documented inflammatory status and systemic complications (B-PCAP, all cases diagnosed by positive blood culture), and the one that is caused by the current pandemic (SARS-CoV-2 pneumonia, all cases diagnosed by positive RT-PCR) and which has also been related to exaggerated systemic inflammation. 2) The type of population studied. Specifically, for both types of pneumonia, we only included immunocompetent patients. This has allowed us to avoid the confounding effect of immunosuppression. 3) The size of sample and the multicenter design of the study. To our knowledge, this is among the largest series published on this topic including data of both types of pneumonia prospectively collected.

The results of this study illustrate that there are clear differences between the clinical presentation of B-PCAP and SARS-CoV-2 pneumonia. B-PCAP can be considered the clear example of classic pneumonia, in which patients present with a history of a few days of typical symptoms, showing high severity on physical examination and laboratory parameters and unilobar involvement on X-ray. In contrast, SARS-CoV-2 pneumonia was observed to have a more dormant clinical course, bilateral lung involvement but higher in-hospital mortality. Few studies have previously compared COVID-19 with other types of pneumonia and all the previous series compared SARS-CoV-2-positive with SARS-CoV-2-negative pneumonia, without specifying the aetiology in the latter case (Tian et al., 2020; Zhao et al., 2020; Zhou et al., 2020). Furthermore, they have included few cases, and just compared the groups in terms of general characteristics and in-hospital course. None of them performed and compared multivariate analysis of severity or survival curves.

Our study confirms the underestimation of the risk of death from viral pneumonia obtained with CURB-65 and PSI scores reported by previous studies (Guo et al., 2019; Nguyen et al., 2020). In our series, these severity scales were not useful for identifying severe patients in SARS-CoV-2 pneumonia, as among patients with this type of pneumonia, just 28.9% of those admitted to the ICU had high-risk PSI scores and 29.9% high-risk CURB-65 scores, but 23.9% died during hospital admission. Moreover, in the entire sample of SARS-CoV-2 pneumonia, only 21.2% of the patients were identified as high risk by the PSI and 23.4% as high risk by the CURB-65 and the in-hospital mortality rate was 10.8%. Wynants et al. 2020 have previously published a systematic review of prediction models for COVID-19 and they concluded that they were unable to recommend any of them for use in clinical practice.

In this study, we have observed that, although B-PCAP patients have worse clinical presentation and laboratory findings, the in-hospital mortality was much higher in SARS-CoV-2 pneumonia. The prognosis of pneumococcal pneumonia has improved in recent years due to new vaccines (Whitney et al., 2003), early diagnosis, and improvements in treatment (Gattarello et al., 2014). In contrast, SARS-CoV-2 pneumonia is a new illness and there is currently no specific antiviral treatment. Furthermore, although vaccines against COVID-19 are being administered in most countries, herd immunity has not yet been achieved. Moreover, the effectiveness of the vaccines is not the same in all patients and the duration of the immunity produced by the vaccine is not well known (Altawalah, 2021). The inflammatory response also plays an important role in COVID-19-related mortality. Previous research has suggested that excessive immune response triggers pathogenesis in other severe viral types of pneumonia, like influenza and SARS (Van den Brand et al., 2014). It has also been documented that SARS-CoV-2 pneumonia triggers a strong innate inflammatory immune response which leads to a cytokine storm that causes acute respiratory distress syndrome (Ye et al., 2020; Xu et al., 2020).We have not found in-hospital mortality in COVID-19 patients to be associated with lymphopenia, unlike Zheng et al, 2020, who did find this association in a meta-analysis analysing risk factors of critical COVID-19 cases. This is despite the fact that the lymphocyte count on admission in our patients with SARS-CoV-2 pneumonia was low and similar to that documented by previous studies (Richardson et al., 2020) though curiously, the median lymphocyte count was even lower among our patients with B-PCAP than among our SARS-CoV-2 pneumonia patients. These results indicate lymphopenia is associated with severity in any type of pneumonia and is not specific for SARS-CoV-2 as it has previously been reported (Mendez et al., 2019).

In this study, we have observed two distinct mortality mechanisms in the two types of pneumonia. In B-PCAP, our predictive model related mortality to systemic complications (hyponatremia, septic shock and neurological complications), lower respiratory reserve (COPD) and high respiratory rate; these risk factors have previously been associated with mortality (Naucler et al., 2013), or are currently included in pneumonia severity scores (Fine et al., 1999; Lim et al., 2003). Chest pain and purulent sputum production were found to be protective factors for mortality in B-PCAP, probably because they were alarm symptoms that prompted the patient to seek medical attention and start treatment earlier (Fine et al., 1996). In contrast, in the SARS-CoV-2 pneumonia, mortality was more closely related to an exaggerated inflammatory response (BUN≥30mg/dl and neutrophilia) or respiratory failure (respiratory rate ≥30/min, oxygen saturation <90% and bilateral lung involvement). Like in previous studies (Berenguer et al., 2020; Gallo et al., 2021), advanced age, altered mental status, heart and liver diseases were also associated with in-hospital mortality and they also indicated worse baseline status. Further, septic shock was predictive of mortality, likely because it was related to bacterial superinfection; although microbiological etiology data were not available. Pleural effusion was also related to in-hospital mortality, as it indicates severe inflammation and could be associated with viral pleuritis, bacterial superinfection or congestive heart failure (Zhan et al., 2021). Seven or more days of symptoms at hospital admission was found to be protective factors for mortality in SARS-CoV-2 pneumonia, as it has previously been reported (Ciceri et al., 2020), probably because the patient is admitted at a later stage of the disease in which the risk of worsening is lower or because the disease is milder and it takes longer to show severe symptoms.

We have found significant differences in the timing of in-hospital death between the groups. In B-PCAP, in-hospital death occurred in the first few days after admission. As has previously been observed, pneumococcal mortality tends to be observed early, as prompt adequate targeted treatment improves outcomes in these patients (Garnacho-Montero et al., 2010). In contrast, in SARS-CoV-2 pneumonia, survival started to decrease from day4-5 of admission, this corresponding to day 10-12 after the onset of symptoms, when the exaggerated inflammatory phase started (Siddiqi and Mehra, 2020).

Finally, regarding patients admitted to the ICU, we observed that the ICU admission rate was lower in the SARS-CoV-2 pneumonia group, but they had a longer ICU stay and greater need for IMV. These data reinforce the association of COVID-19 severity with respiratory failure while B-PCAP severity was also associated with septic shock or other complications. All the complications were more often observed in the B-PCAP group, expect thromboembolic complications, which were more frequent in SARS-CoV-2 pneumonia. Coagulopathy has previously been documented in severe COVID-19 patients, and this could lead to thromboembolic complications (Levi et al., 2020). Predictive factors associated with ICU admission in B-PCAP were factors previously associated with severity (smoking, tachypnea, hypotension, high blood urea nitrogen levels, respiratory failure or bilateral lung involvement). Older age had a negative association with ICU admission: as previous studies have documented, this indicates the negative influence of advanced age on eligibility for ICU admission (Boumendil et al., 2012; Ruiz et al., 2017). Leucocytosis was identified as protective against ICU admission; whereas leukopenia indicates abnormalities in the host's inflammatory response associated with increased susceptibility to severe disease and mortality (Hanada et al., 2016). Once again, in SARS-CoV-2 pneumonia, respiratory failure (tachypnea, and Sat O2<90%) and cytokine storm (lymphopenia) were related to severity and ICU admission. Old age and nursing home residence were negatively associated with ICU admission; as in B-PCAP, such patients were likely not eligible for ICU admission because of their poor baseline status.

This study has some limitations. This was an observational study and data on the two types of pneumonia were prospectively collected in different time periods. We have compared B-PCAP cases registered over 20 years with SARS-CoV-2 cases registered in 10 months (March-December 2020), and this could introduce differences related to external uncontrollable factors. On the other hand, we have only included 1st and 2nd wave COVID-19 patients. This may be a limitation but also a strength, because it has allowed us to eliminate the bias of the pandemic effect that would have had to analyze only the first wave patients; and avoids the effect of the vaccination of subsequent waves (in Spain it started in January 2021). Further, in B-PCAP, we did not gather data on and, hence, were not able to compare laboratory data that seem to be commonly altered in SARS-CoV-2 pneumonia (i.e., D-dimer, lactate dehydrogenase or ferritin). Furthermore, there are some therapies like high-flow oxygen therapy or extracorporeal membrane oxygenation that have started to be used in recent years and we have not been able to compare their effect in the two groups. On the other hand, as SARS-CoV-2 pneumonia has caused the pandemic with millions of cases in a short time, we consider our approach to be the only way to compare patients with this type of pneumonia with a similarly sized sample of patients with B-PCAP.

Conclusions

We have examined differences between general characteristics, clinical presentation and in-hospital course of patients with B-PCAP and SARS-CoV-2pneumonia and analysed factors associated with in-hospital mortality and ICU admission in both groups. This study has demonstrated differences in the behaviour of the two entities, which may facilitate differential diagnosis and allow us to provide differentiated treatment. Although patients with B-PCAP have higher severity on admission and ICU admission rate, in-hospital mortality associated with SARS-CoV-2 pneumonia was higher and occurred later during hospital admission. Our results reinforce the need for new prognosis scales and effective treatment for SARS-CoV-2 pneumonia.

Conflict of interests: none. The authors declare they have no conflict of interest.

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Authors' contributions: LSF and LAR take the responsibility of the manuscript as a whole. LSF, LAR, RZJ, RMV, RMO and PPE conceived and designed the study. AUE, PGH, PGJ, ETH, RMO, and LAR enrolled patients and collected and compiled data. SPF performed the statistical analysis. LSF, RZJ, LAR, RMO, ATM, PPE, and RMV analyzedand interpreted the data. LSF, RZJ, and LAR wrote the manuscript. RMV, RMO, ATM, AUE and PPE commented and revised the report. All authors read and approved the final manuscript.

Ethical Approval: This study was approved by the corresponding ethics committee (code PI2020083) and conducted in accordance with the principles of the Declaration of Helsinkion research in humans.

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Table 1: General characteristics and in-hospital course overall and stratified by pneumonia aetiology

	All patients (n=2224)	Pneumococcal bacteraemic pneumonia (n=663)	SARS-CoV-2 pneumonia (n=1561)	p
Demographic characteristics				
Sex (male)	1367 (61.5%)	427 (64.4%)	940 (60.2%)	0.071
Age ≥65 years	1005 (45.1%)	338 (51%)	667 (42.7%)	0.010
Active smoker	293 (13.3%)	220 (33.2%)	73 (4.8%)	<0.001
Alcoholism	218 (11.3%)	115 (17.6%)	103 (8.1%)	<0.001
Nursing home resident	89 (4%)	18 (2.7%)	71 (4.6%)	0.057
Comorbid conditions				
Comorbidities, yes	1332 (59.9%)	394 (59.4%)	938 (60.1%)	0.807
Hypertension	914 (41.2%)	280 (42.5%)	634 (40.6%)	0.440
Diabetes mellitus	400 (18%)	109 (16.4%)	291 (18.6%)	0.240
Dyslipidaemia	694 (31.3%)	156 (23.7%)	538 (34.5%)	<0.001
Heart disease	412 (18.6%)	173 (26.3%)	239 (15.3%)	<0.001
Cerebrovascular disease	92 (4.8%)	42 (6.3%)	50 (3.9%)	0.025
Chronic obstructive pulmonary disease	218 (9.8%)	120 (18.1%)	98 (6.3%)	<0.001
Liver disease	90 (4.1%)	42 (6.3%)	48 (3.1%)	0.001
Chronic severe renal disease	164 (7.3%)	45 (6.8%)	119 (7.6%)	0.548
Neoplastic disease	143 (6.4%)	52 (7.8%)	91 (5.8%)	0.094
Clinical characteristics				
Duration of symptoms (days) Median (IQR)	6 (3-8)	3 (2-5)	7 (5-10)	<0.001
Altered mental status	153 (6.9%)	70 (10.6%)	83 (5.3%)	<0.001
Fever	1649 (74.5%)	539 (82.7%)	1110 (71.1%)	<0.001
Cough	1627 (73.6%)	502 (77%)	1125 (72.2%)	0.022
Purulent sputum production	361 (16.3%)	300 (46%)	61 (3.9%)	<0.001
Dyspnoea	1196 (54%)	384 (58.9%)	812 (52%)	0.004
Chest pain	544 (24.6%)	338 (51.8%)	206 (13.2%)	<0.001
Physical examination				
Temperature >39ºC	126 (5.7%)	83 (12.5%)	43 (2.8%)	<0.001
Respiratory rate ≥30 breaths /min	299 (15.4%)	172 (26.4%)	127 (9.9%)	<0.001
Heart rate > 125beats/min	161 (7.3%)	115 (17.3%)	46 (3%)	<0.001
Systolic blood pressure <90mmHg	83 (3.8%)	59 (8.9%)	24 (1.6%)	<0.001
Sat O2 < 90%	412 (18.6%)	216 (33%)	196 (12.6%)	<0.001
Laboratory and radiological findings				
Glucose (Median-IQR) mg/dL	114 (100-142)	129 (107-166)	110 (99-130)	<0.001
Blood urea nitrogen ≥30 mg/dl	492 (22.2%)	303 (45.8%)	189 (12.1%)	<0.001
Sodium <130 mmol/L	83 (3.7%)	63 (9.5%)	20 (1.3%)	<0.001
Haematocrit <30%	52 (2.3%)	19 (2.9%)	33 (2.1%)	0.361
C-reactive protein ≥150 mg/L	449 (22.7%)	171 (40.1%)	279 (17.9%)	<0.001
Platelet count x10^3/µL (Median-IQR)	194 (150-246)	197 (159-246)	192 (148-246)	0.193
White blood cell count/µL (Median-IQR)	7090 (5115-11408)	14170 (9600-20100)	6170 (4730-8070)	<0.001
Neutrophils/µL (Median-IQR)	5400 (3590-9514)	12558 (7900-17676)	4500(3250-6240)	<0.001
Lymphocytes/µL (Median-IQR)	920 (640-1299)	710 (417-1170)	990(715-1330)	<0.001
Neutrophil/lymphocyte ratio (Median-IQR)	5.94 (3.4-12.1)	15.5 (9.33-26.6)	4.37 (2.93-7.42)	<0.001
Lymphocyte/C-reactive protein ratio (Median-IQR)	14.4 (5.82-36.2)	8.05 (2.43-24.6)	15.9 (7.08-42.5)	<0.001
Lung involvement on X-ray				
Single lobe	783 (35.4%)	424 (64.7%)	359 (23.1%)	<0.001
Unilateral multilobe	215 (9.7%)	120 (18.3%)	95 (6.1%)	<0.001
Bilateral	1228 (55.5%)	111 (16.9%)	1117 (71.8%)	<0.001
Pleural effusion	154 (6.9%)	119 (17.9%)	35 (2.2%)	<0.001
Severity				
Pneumonia Severity Index IV-V	695 (31.3%)	364 (55.5%)	331 (21.2%)	<0.001
CURB-65 ≥2	774 (35.2%)	409 (64.2%)	365 (23.4%)	<0.001
In-hospital course				

Admission to intensive care unit Length of ICU stay (days)(Median-IQR)	386 (17.4%) 13 (6-21)	185 (27.9%) 5 (3-11)	201 (12.9%) 14 (7-24)	<0.001 <0.001
Need for mechanical ventilation Length of IMV days (Median-IQR)	209 (9.4%) 14 (8-22)	67 (10.1%) 10 (4-18)	142 (9.1%) 13 (8-21)	0.505 0.563
Neurological complications	94 (4.2%)	59 (8.9%)	35 (2.2%)	<0.001
Renal complications	259 (11.7%)	148 (22.4%)	111 (7.1%)	<0.001
Cardiac complications	212 (9.7%)	106 (16.1%)	106 (6.9%)	<0.001
Thromboembolic complications	55 (2.8%)	5 (0.8%)	50 (3.9%)	<0.001
Haematological complications	80 (3.9%)	58 (10.1%)	22 (1.5%)	<0.001
Septic shock	150 (6.8%)	116 (17.7%)	34 (2.1%)	<0.001
Outcomes				
In-hospital mortality	214 (9.6%)	45 (6.8%)	169 (10.8%)	0.004
30-day readmission	93 (5.3%)	18 (2.7%)	75 (6.9%)	<0.001
Length of hospital stay (Median-IQR)	8 (5-13)	7 (4-10)	9 (5-14)	<0.001

IQR=interquartile range

Table 2: Differences between patients admitted to the ICU with B-PCAP vs SARS-CoV-2 pneumonia

	All patients (n=386)	Pneumococcal bacteraemic pneumonia (n=185)	SARS-CoV-2 pneumonia (n=201)	p
Demographic characteristics				
Sex (male)	272 (72.5%)	131 (70.8%)	141 (70.1%)	0.976
Age ≥65 years	124 (32.1%)	68 (36.8%)	56 (27.9%)	0.854
Active smoker	95 (24.8%)	87 (47%)	8 (4%)	<0.001
Alcoholism	69 (20.1%)	51 (27.9%)	18 (11.2%)	<0.001
Nursing home resident	6 (1.5%)	4 (2.2%)	2 (1%)	0.432
Comorbid conditions				
Comorbidities, yes	243 (63%)	101 (54.6%)	142 (70.6%)	0.002
Hypertension	159 (41.3%)	64 (34.8%)	95 (47.3%)	0.017
Diabetes mellitus	70 (18.1%)	22 (11.9%)	48 (23.9%)	0.003
Dyslipidaemia	115 (29.9%)	42 (22.8%)	73 (36.3%)	0.005
Heart disease	54 (14%)	27 (14.7%)	27 (13.4%)	0.839
Cerebrovascular disease	10 (2.9%)	7 (3.8%)	3 (1.9%)	0350
Chronic obstructive pulmonary disease	54 (14%)	39 (21.1%)	15 (7.5%)	<0.001
Liver disease	24 (6.2%)	20 (10.8%)	4(2%)	0.001
Chronic severe renal disease	21 (5.4%)	9 (4.9%)	12 (5.9%)	0.800
Neoplastic disease	21 (5.4%)	10 (5.4%)	11 (5.5%)	1
Clinical characteristics				
Duration of symptoms (days) Median (IQR)	5 (3-7)	3 (2-5)	7 (5-9)	<0.001
Altered mental status	38 (9.8%)	25 (13.5%)	13 (6.5%)	0.032
Fever	292 (76.2%)	143 (78.6%)	149 (74.1%)	0.368
Cough	293 (76.5%)	139 (76.4%)	154 (76.6%)	1
Purulent sputum production	88 (23%)	82 (45.1%)	6 (3%)	<0.001
Dyspnoea	255 (66.6%)	124 (68.1%)	131 (65.2%)	0.614
Chest pain	109 (28.5%)	92 (50.5%)	17 (8.5%)	<0.001
Physical examination				
Temperature >39ºC	34 (9.04%)	24 (13%)	10 (5.2%)	0.015
Respiratory rate ≥30breaths/min	143 (40.6%)	87 (47.8%)	56 (32.9%)	0.006
Heart rate > 125 beats/min	63 (16.3%)	53 (28.6%)	10 (5%)	<0.001
Systolic blood pressure <90mmHg	47 (12.1%)	44 (23.8%)	3 (1.4%)	<0.001
Sat O2 < 90%	155 (40.2%)	93 (50.8%)	62 (30.8%)	0.180
Laboratory and radiological findings				
Glucose (Median-IQR) mg/dL	120 (102-150)	120 (99-153)	121 (106-147)	0.363
Blood urea nitrogen ≥30 mg/dl	139 (36%)	119 (64.3%)	20 (9.9%)	<0.001
Sodium <130 mmol/L	34 (8.8%)	28 (15.1%)	6 (2.9%)	0.001
Haematocrit<30%	11 (2.8%)	5 (2.7%)	6 (2.9%)	0.544
C-reactive protein≥ 150 mg/L	108 (33.5%)	54 (44.3%)	54 (27%)	0.002
Platelet count x10^3/µL (Median-IQR)	187 (143-236)	182 (141-227)	191 (143-239)	0.405
White blood cell count/µL (Median-IQR)	7750 (5200-12100)	11300 (6230-16300)	6595 (5032-8418)	<0.001
Neutrophils/µL (Median-IQR)	6420 (3892-10902)	10081 (5100-14626)	5105 (3678-7192)	<0.001
Lymphocytes/µL (Median-IQR)	735 (430-1082)	564 (300-1064)	805 (598-1090)	<0.001
Neutrophil/lymphocyte ratio (Median-IQR)	9.83 (5.33-18.6)	15.5 (7.89-26.9)	6.85 (4.27-10.5)	<0.001
Lymphocyte/C-reactive protein ratio (Median-IQR)	7.5 (2.9-17.4)	4.59 (1.62-15.7)	9.4 (4.36-17.6)	<0.001
Lung involvement on X-ray				
Single lobe	91 (23.8%)	63 (34.6%)	28 (13.9%)	<0.001
Unilateral multilobe	63 (16.4%)	56 (30.8%)	7 (3.5%)	<0.001
Bilateral	231 (60.3%)	63 (34.6%)	168 (83.6%)	<0.001
Pleural effusion	41 (10.6%)	38 (20.5%)	3 (1.5%)	<0.001
Severity				
Pneumonia Severity Index IV-V	186 (48.3%)	128 (69.6%)	58 (28.9%)	<0.001
CURB-65 ≥2	197 (53.8%)	137 (75.7%)	60 (29.9%)	<0.001
In-hospital course				

Need for mechanical ventilation Length of IMV days (Median-IQR)	207 (53.6%) 13 (7.25-21)	67 (36.2%) 10 (4-18)	140 (69.7%) 13 (8-21)	<0.001 0.563
Complications				
Neurological complications Stroke	48 (12.5%) 1 (0.3%)	29 (15.8%) 0	19 (9.6%) 1 (0.7%)	0.093 0.445
Renal complications	128 (33.4%)	89 (48.4%)	39 (19.6%)	<0.001
Cardiac complications	90 (23.8%)	51 (27.9%)	39 (20%)	0.094
Thromboembolic complications	26 (7.3%)	4 (2.2%)	22 (12.9%)	<0.001
Haematological complications	52 (14.6%)	46 (27.9%)	6 (3.1%)	<0.001
Septic shock	130 (33.9%)	107 (57.8%)	23 (11.6%)	<0.001
Outcomes				
In-hospital mortality	72 (18.7%)	24 (13%)	48 (23.9%)	0.009
30-day readmission	11 (3.79%)	5 (2.7%)	6 (5.7%)	0.218
Length of hospital stay (Median-IQR)	18 (10-33)	12 (7-20)	25 (16-41)	<0.001

IQR=interquartile range

Table 3: Multivariate Cox regression of factors associated with in-hospital mortality in patients hospitalized with bacteraemic pneumococcal pneumonia and SARS-CoV-2 pneumonia

Bacteraemic pneumococcal pneumonia			SARS-CoV-2 pneumonia		
	OR (95% CI)	**p-value**		**OR (95% CI)**	**p-value**
Chronic obstructive pulmonary disease	2.38 (1.19- 4.78)	0.015	Age ≥65 years	4.777 (2.814-8.111)	<0.001
Purulent sputum production	0.4 (0.2-0.79)	0.009	Heart disease	1.587 (1.077-2.341)	0.02
Chest pain	0.41 (0.19-0.88)	0.022	Liver disease	2.365 (1.199-4.662)	0.013
Respiratory rate ≥30 breaths/min	2.9 (1.43-5.89)	0.003	Altered mental status	2.464 (1.586-3.827)	<0.001
Sodium <130 mmol/L	3.26 (1.37-7.81)	0.008	≥ 7 days of symptoms	0.464 (0.314-0.685)	<0.001
Neurological complications*	7.25 (3.52-14.93)	<0.001	Respiratory rate ≥30 breaths/min	2.117 (1.362-3.289)	<0.001
Septic shock	2.18 (1.06-4.48)	0.035	Sat O2 < 90%	1.599 (1.045-2.477)	0.03
			Blood urea nitrogen ≥ 30mg/dl	1.864 (1.236-2.81)	0.003
			Neutrophil count/μL/10000**	1.052 (1.018-1.086)	0.002
			Bilateral lung involvement	1.868 (1.142-3.056)	0.013
			Pleural effusion	2.894 (1.282-6.536)	0.011
			Septic shock	2.781 (1.703-4.542)	<0.001

**Neurological complications: stroke, delirium and/or seizure

**Neutrophil count is presented for each 10000-unit increase.

OR: Odds ratio. CI: confidence interval

Table 4: Multivariate logistic regression of factors associated with ICU admission in patients hospitalized with bacteraemic pneumococcal pneumonia and SARS-CoV-2 pneumonia

Bacteraemic pneumococcal pneumonia			SARS-CoV-2 pneumonia		
	OR (95% CI)	**p-value**		**OR (95% CI)**	**p-value**
Age ≥65*	0.28 (0.17-0.47)	<0.001	Nursing home resident	0.132 (0.002-0.486)	0.009
Active smoker	2.09 (1.29-3.4)	0.003	Age ≥65 years*	0.563 (0.375-0.833)	0.005
Respiratory rate ≥30 breaths/min	3.39 (2.11-5.46)	<0.001	Respiratory rate ≥30 breaths/min	3.09 (1.891-5)	<0.001
Systolic blood pressure <90mmHg	12.53 (6.09-27.2)	<0.001	Sat O2 < 90%	4.483(2.812-7.125)	<0.001
Sat O2 < 90%	2.39 (1.46-3.92)	<0.001	Lymphocytes/ µL/1000***	0.364 (0.231-0.557)	<0.001
Blood urea nitrogen ≥30 mg/dl	3.45 (2.15-5.63)	<0.001			
White blood cell count/µL/1000**	0.95 (0.92-0.98)	<0.001			
Bilateral lung involvement	3.17 (1.84-5.48)	<0.001			

*It indicates the negative influence of advanced age on eligibility for ICU admission

**White blood cell count is presented for each 1000-unit increase.

*** Lymphocytes are presented for each 1000-unit increase.

OR: Odds ratio. CI: confidence interval

Figure 1: 30-day Kaplan-Meier survival curve for patients with B-PCAP and SARS-CoV-2 pneumonia